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Bleeding Risk Factors in Chronic Oral Anticoagulation With Acenocoumarol

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We studied major bleeding complications, death related to hemorrhage, and tried to identify predisposing factors for bleeding in outpatients treated with acenocoumarol. We evaluated 811 outpatients attending a specialized anticoagulant therapy unit. The intended INR range was 3.5–4.5 for mechanical heart valve replacement (*N* = 384) and 2.0–3.0 for other indications (*N* = 427). The variability of INR for the total follow-up and the 2 months before the hemorrhage was calculated. The total follow-up was 1,963.26 years with 27,321 control tests. We observed 47 major bleeding episodes, including 2 fatal (central nervous system hemorrhages), in 37 patients. 49.5% of the patients had underlying diseases. The rate of major and fatal hemorrhage was 2.39 and 0.10 episodes per 100 patients year, respectively. Hemorrhagic complications were more frequently observed in patients with a more intense intended range (8.2% in the INR 3.5–4.5 group vs. 1.5% in the 2.0–3.0 INR group). The risk of major bleeding increased in patients with an achieved INR higher than 6 and in those with higher INR variability during follow-up. The estimated probability of bleeding also increased with time: it was 0.102% at 78 months, and at the beginning of therapy it was 0.006% and 0.007% at 1 and 4 months, respectively. The intensity of anticoagulation and the deviation of the INR from the target are the most important risk factors for bleeding in patients taking acenocoumarol. Monitoring the variability of INR can help identifying patients predisposed to bleeding. However, the screening for underlying disease should always be performed. Am. J. Hematol. 63:192–196, 2000. © 2000 Wiley-Liss, Inc.

Key words: acenocoumarol; oral anticoagulant therapy; hemorrhage; bleeding risk factors

INTRODUCTION

Chronic anticoagulation is the therapy of choice for an increasing variety of congenital and acquired thromboembolic disorders. Bleeding continues to be the most serious complication. Although there have been many studies that tried to identify independent risk factors for hemorrhage, controversy still remains [1–3].

Some authors found an increasing tendency for hemorrhagic complications in older patients [1,4,5], while others did not consider age by itself to be an independent risk factor [3,6,7]. The presence of one or more comorbid conditions has been considered as a risk indicator [3,6]. The conditions that had been taken into account are atrial fibrillation, cerebrovascular disease, chronic heart failure, diabetes, hypertension, cancer, peptic ulcer, and chronic heart failure [1,6–10].

To estimate the risk factors for bleeding according to the treatment itself, van der Meer [4] developed the bleeding risk index and Fihn analyzed the effect of the variability of the patient's Prothrombin time from the target over the time and found that greater deviations from the target were associated with an increased bleeding tendency [3,7]. The incidence of hemorrhagic complications was inversely related to the duration of anticoagulation [5,6,11], although this finding was not confirmed in other reports [12,13].

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We conducted a retrospective cohort study of outpatients who received acenocoumarol therapy without aspirin in a specialized anticoagulant therapy unit. Our objectives were to study major bleeding complications, death related to hemorrhage, and predisposing factors for bleeding, those depending on the patients characteristics as well as the ones depending on the treatment itself, emphasizing the similarity and differences with warfarin therapy.

MATERIALS AND METHODS

Patients

The study included consecutive outpatients anticoagulated with acenocoumarol. The only exclusion criteria were the use of any antiplatelet agent or anticoagulant therapy for less than 4 weeks.

We examined the computerized medical records of all patients who received acenocoumarol since August 1988 until October 1995. To define risk groups we recorded age, sex, indications for anticoagulation, co-morbid conditions (including previous coagulation disorders), concomitant medications, INR of every control, and all hemorrhagic events (date, magnitude, site of bleeding, precipitating event such as underlying disease or change in current medications, and INR whenever it was available). An INR was considered related to the event if it was obtained the day of the hemorrhage or within the previous week.

Control of Anticoagulation

Anticoagulation therapy was started with 1 or 2 mg of acenocoumarol according to the basal prothrombin time (PT) for 3 days, then the dose was adjusted. Once the target was achieved, patients came for control every 30 days; if a change in the dose was made, the control was scheduled with a shorter interval. Oral anticoagulation was monitored by PT expressed as international normalized ratio (INR). The thromboplastins used had international sensitivity index (ISI) under 1.05. Two intensities of anticoagulation were included: group 1 ($N = 427$), with intended INR range 2.0–3.0 (mainly atrial fibrillation), and group 2 ($N = 384$), with intended INR range 3.5–4.5 (mechanical heart valve replacement).

We gave extensive instructions to all new patients to monitor changes in patients' habits, co-medications, illnesses, or bleeding complications.

We used the data obtained from Rosendaal's method [14] to calculate time spent within the range and to analyze the influence of variability in anticoagulation therapy with acenocoumarol [3]. For each patient the INR variability of the total follow-up was calculated. We compared the variability of the patients who presented no bleeding complications during their therapy to the variability of those with complications.

TABLE I. Patient Characteristics

Sex	
Female	370
Male	441
Age (years)	
Median	58.5
Range	5–88
Follow up	
Medium (months)	30
Total (years)	1963.23 years
Diagnosis (*N*)	
Heart valve prosthesis	384
Atrial fibrillation	213
Cardiomyopathy	135
Valvular heart disease	90
Deep venous thrombosis/pulmonary embolism	87
Endocavitary thrombosis	47
Others	48

Hemorrhagic Complications

Major hemorrhages included the fatal events, those requiring transfusion, hospitalization, and the gastrointestinal, central nervous system, or ocular (with blindness) hemorrhages. Major hemorrhages were subclassified according to the probability of a precipitating event as "without cause" and "with known cause" (including those with diagnosed underlying disease and those with recurrent bleeding in one site in spite of an extensive negative workup for an underlying lesion). Minor bleeding complications were those episodes that were not life threatening, requiring no additional investigation and no treatment, but that were remarkable enough to lead the patient to report it or to consult for that reason.

Statistical Considerations

Comparison of qualitative variables was performed using Pearson's chi-square test or Fisher's exact test, as indicated. Comparison of quantitative variables was performed with non-parametric univariate analysis of Kruskal–Wallis [15]. Analysis of hemorrhage risk was performed according to Kaplan–Meier methods [16], and a log-rank test [17] was used for intergroup comparisons. Cox regression models [18] were used as multivariate test to determine the relationship among these parameters in relation to risk of hemorrhage. The level considered significant was $P < 0.05$. All the analysis was performed with the Stata statistical package.

RESULTS

Patient Characteristics

We studied 811 consecutive outpatients anticoagulated with acenocoumarol. Patients characteristics are listed in Table I. The most common primary indications for anticoagulation were mechanical heart valve prosthesis and atrial fibrillation (Table I). Two reasons for anticoagula-

TABLE II. Site of Major Hemorrhage

Site of bleeding	Events (*N*)
Gastrointestinal	26
Epistaxis	10
CNS	5 (2 fatal)
Metrorrhagia	3
Peritoneal	1
Haemoptysis	1
Psoas hematoma	1

tion were found in 187 patients (23%); 7 patients (0.9%) had three reasons for treatment.

Co-morbid Conditions, Coagulation Disorders, and Concomitant Drugs

The most frequent co-morbid diseases were as follows: chronic heart failure ($N = 66$), stroke ($N = 62$), myocardial infarction ($N = 46$), hypertension ($N = 40$), neoplasm ($N = 25$), hypercholesterolemia ($N = 24$), gout ($N = 22$), and others ($N = 26$). Thirty-five patients (35/811) had co-morbid gastrointestinal diseases: 23/811 patients (2.8%) suffered from gastritis and 12/811(1.4%) had peptic ulcer; 85.7% of them (30/35) had a previous gastrointestinal hemorrhage. Forty patients (4.9%) had mucocutaneous bleeding history before anticoagulation, and 18 patients (2.2%) had either von Willebrand's disease or low platelet retention to glass beads.

Most patients (53%) received no additional drugs, 237 patients (29%) received just one, 117 patients (14%) received two, and the rest were under treatment with three to five drugs.

Control of Anticoagulation

The total number of INR tests was 27,321. Median INR variability (SD) was 0.93 (0.58). Median INR (SD) was 3.7 (1.6) in group 1 and 2.7 (1.2) in group 2. The low-intensity anticoagulation group remained within the target 56.2% of time and the high-intensity group 32.5% ($P < 0.0000$). The first group was above the intended range 27.8% of the time and below 16%. Patients with higher range were above 28.5% and below 39% of the time.

Bleeding Complications

We observed 47 major hemorrhages in 37 patients (Table II) and 254 minor events in 187 patients. The rate of major hemorrhage was 2.39 (95% CI 1.78–3.21) episodes per 100 patient-years, the rate of fatal episodes was 0.10 (95% CI 0.02–4.2) per 100 patient-years. The estimated probability of bleeding was 0.006% (95% CI 0.985–0.997) at 1 month, 0.007% (95% CI 0.984–0.997) at 4 months, and 0.102% (95% CI 0.84–0.93) at 78 months (Fig. 1). Median age of patients who presented

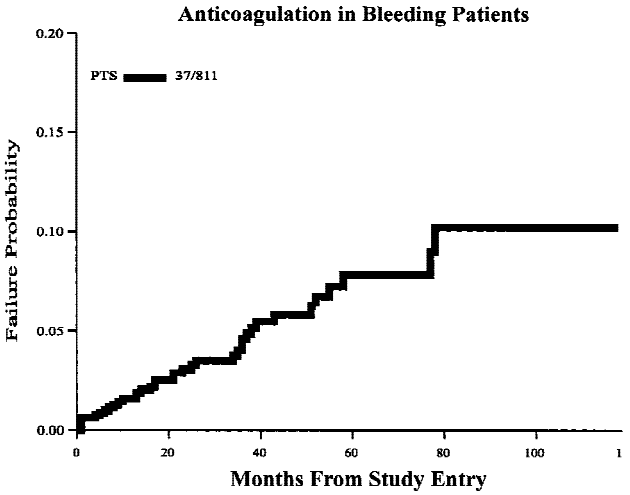

Fig. 1. Actuarial estimated risk of bleeding in 811 patients.

major bleeding complications was 59 years; 51.3% ($N = 20$) were male.

Patient-Related Risk Factors

Cox regression analysis showed that age and sex were not significant factors predisposing to hemorrhage ($P = 0.536$ and 0.715, respectively). We observed a higher incidence in major bleeding among the patients with chronic heart failure, hypertension, and past history of stroke which was significant ($P = 0.0020$, 0.0320, and 0.0350, respectively) but only in the higher target group. In 23 major events (49%) an underlying disease was diagnosed, the remaining episodes (24/47) were considered without cause. Six patients had more than one major event and all of them had an underlying disease.

Treatment-Related Risk Factors

The INR was available in 25 major hemorrhage episodes: 12 were beyond and 10 were under the target INR. The INR variation of the patients with major hemorrhage was 1.04 (0.74), it increased when the two controls before the event where considered though it was not significant ($P = 0.2$).

The percentage of patients with major events was higher in the high-intensity target group (8.2 vs. 1.5%; $P < 0.0000$). The relative risk of bleeding according to INR range shows an increasing risk when INR is greater than 6 (Table III).

Fatal Hemorrhage

Two of the major episodes were fatal and due to central nervous system bleeding. Both patients had mechanical heart valve replacement in aortic position. One of them was a woman, 50 years old, with post-traumatic subdural hematoma; the INR value was not available. The other patient was a male, 67 years old, with a history

TABLE III. Risk of Bleeding Complications for 100 Patient-Years

INR range	Years	N	Incidence rate per 100 years observation
1.0–1.9	179.79	2	1.11 (95% CI 0.19–4.4)
2.0–2.9	707.23	8	1.13 (95% CI 0.53–2.3)
3.0–3.9	550.21	3	0.55 (95% CI 0.14–1.7)
4.0–4.9	309.27	2	0.65 (95% CI 0.11–2.6)
5.0–5.9	134.00	1	0.75 (95% CI 3.9–47)
6.0–6.9	47.71	1	2.10 (95% CI 0.11–13)
7.0–7.9	13.32	3	17.32 (95% CI 4.5–55)
8.0–8.9	8.89	1	11.24 (95% CI 0.55–72)
≥9.0	8.84	4	45 (95% CI 14–123)
Total	1,963.26	25	1.27 (95% CI 0.84–1.9)

of stroke and lung cancer. The INR at the time of the hemorrhage was 9.13.

Concomitant Drugs

Patients that presented hemorrhagic complications were not taking more medications than the ones that did not bleed; moreover, 19 patients (50%) received no drugs, and 9 (24%) were treated with only one medication besides acenocoumarol.

DISCUSSION

During the past few years important achievements have been accomplished in the field of anticoagulation therapy. Most published information is related to the use of warfarin [1–4,6–8,10], and there are few studies with acenocoumarol [19,22,23]. We evaluated a large series of patients receiving acenocoumarol monitored by INR in specialized anticoagulation clinics with the purpose of analyzing major bleeding complications, death related to hemorrhage, and risk factors for bleeding.

Our rate of major and fatal bleeding events (2.39 and 0.10 per 100 patient-years, respectively) is similar to the observed in other studies [1,5]. The ISCOAT [11], a study with similar follow-up, shows a lower rate of major bleeding but more fatal events (1.1 and 0.25 per 100 patient-years). There is controversy about age and sex as independent risk factors [4,5,11,12]. We observed no difference in the incidence of major hemorrhage according to sex or age; in regard to age one of the reasons could be that we have few patients older than 70 years.

Hylek and Singer [8] reported several independent risk factors for intracranial bleeding in patients taking warfarin: prothrombin time ratio, age, cerebrovascular disease, and prosthetic heart valve. In our series, two patients with mechanical heart valve replacement died from central nervous system hemorrhage; one of them had a history of cerebrovascular disease and lung cancer, but he was excessively anticoagulated as well. However, only two episodes do not allow us to make any conclusions.

Co-morbid conditions seem to be a predisposing factor only in patients with more intense anticoagulation. This raises the question of whether co-morbid states truly play a role in the genesis of hemorrhage.

Many authors suggested that anticoagulation may unmask previously unknown lesions [11,20]. We found predisposing factors related to the bleeding site in 49.5% (23/47) of major episodes, similar results were reported by Landefeld [1]. Meschengieser [19] reported possible predisposing factors in 7/15 patients who received anticoagulation for heart valve prosthesis and presented major bleeding. Our findings can lead to underestimation of the real frequency of organic lesions because, as an outpatient clinic, the work-up for underlying disease was limited in some cases.

Even though it is known that poly-medication may interfere with the anticoagulant's effect [12,21], it did not play a role in the bleeding complications in our patients because most of them received no medications besides acenocoumarol at the moment of the major hemorrhage. Indeed, we gave extensive instructions, and patients were aware to report all new medications to schedule for the next visit or change the dose of acenocoumarol to minimize the risk of drug interactions.

The fact that higher intensity of anticoagulation is related to a greater risk of bleeding is already known from literature [1,4,7,11,12,19]. In a recent prospective study [19] comparing low-dose anticoagulation plus low-dose of aspirin versus high-intensity anticoagulation with acenocoumarol, the rate of gastrointestinal bleeding was more than double in the arm with more intense anticoagulation without aspirin even after the exclusion of patients with predisposing causes. In an inception cohort study, Landefeld et al. [1] analyzed the association between bleeding and prothrombin time (PT); they observed that for each 1.0 increase in the PT, the odds ratio for temporally related major bleeding increased 80%. In agreement with this, Van der Meer [4] studied the influence of the target range on the bleeding risk, showing the influence of increasing target and achieved INR on the risk. The ISCOAT study [11] and Fihn [7] confirmed that the risk of bleeding is higher when INR is higher than 4.5. We found that an INR beyond 6 determines a higher rate of bleeding complications.

Many authors have reported that the risk of bleeding diminishes during the course of therapy [5,6] while others [13] disagree with this observation; our findings are consistent with the latter observation. We found a greater predisposition for bleeding in the patients with longer courses of treatment. One possible explanation for the higher risk at the beginning of therapy could be the longer half-life of warfarin and the use of a loading dose, an issue most authors do not mention; also the lowering of prothrombin time could facilitate the bleeding from an occult organic lesion already present at the time of ini-

tiating anticoagulation. Our findings suggest that the longer the time a patient is exposed to acenocoumarol, greater is the risk to develop hemorrhagic complications during chronic oral anticoagulation.

CONCLUSIONS

To the best of our knowledge, this is the first evaluation of a large series of patients under acenocoumarol with long follow-up from an outpatient clinic. Our rate of major events is similar to that referred for warfarin. We conclude that the intensity of anticoagulation is the most important risk factor for bleeding. Monitoring the deviation of INR may help predict patients at higher risk for bleeding, as it was described in patients on warfarin [3]. However, irrespective of the INR at the time of the hemorrhage, a diagnostic evaluation for underlying disease should be performed.

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REFERENCES

1. Landefeld CS, Beyth RJ. Anticoagulant-related bleeding clinical epidemiology, prediction and prevention. Am J Med 1993;95:315–328.
2. Levine MN, Raskob G, Hirsh J. Hemorrhage complications of long-term anticoagulant therapy. Chest 1995;108:291s–301s.
3. Fihn SD, Mc Donell M, Martin D, Henikoff J, Vermes D, Kent D, White RH. Risk factors for complications of chronic anticoagulation: A multicenter study. Ann Intern Med 1993;118:511–520.
4. van der Meer FJM, Rosendaal FR, Vandenbroucke JP, Briët E. Assessment of a bleeding risk index in two cohorts of patients treated with oral anticoagulants. Thromb Haemost 1996;76:12–16.
5. Steffensen FH, Kristensen K, Ejlersen E, Dahlerup JF, Sorensen HT. Major haemorrhagic complications during oral anticoagulant therapy in a Danish population-based cohort. J Intern Med 1997;242:497–503.
6. Gitter MJ, Jaeger TM, Petterson TM, Gersh BJ, Silverstein MD. Bleeding and thromboembolism during anticoagulant therapy: A population-based study in Rochester, Minnesota. Mayo Clin Proc 1995;70:725–733.
7. Fihn SD, Callhan CM, Martin DC, McDonnell MB, Henikoff JG, White RH. The risk for and severity of bleeding complications in elderly patients treated with warfarin. Ann Intern Med 1996;124:970–979.
8. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. Ann Intern Med 1994;120:897–902.
9. Toulemonde F. The role of individual risk factors in anticoagulant-associated hemorrhages. Sem Thromb Hemostas 1996;22:53–60.
10. Landefeld CS, Goldman L. Major bleeding in outpatients treated with warfarin: incidence and prediction by factors known at the start of outpatient therapy. Am J Med 1989;87:144–152.
11. Palareti G, Leali N, Coccheri S, Poggi M, Manotti C, D'Angelo A, Pengo V, Erba N, Moia M, Ciavarella N, Devoto G, Berettini M, Musolesi S, on behalf of the Italian Study on Complications of Oral Anticoagulant Therapy. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Lancet 1996;348:423–428.
12. Launbjerg J, Egeblad H, Heaf J, Nielsen NH, Fugleholm AM, Ladefoged K. Bleeding complications to oral anticoagulant therapy: Multivariate analysis of 1010 treatment years in 551 outpatients. J Intern Med 1991;229:351–355.
13. Petitti DB, Storm BL, Melmon KL. Duration of anticoagulant therapy and the possibilities of recurrent thromboembolism and hemorrhage. Am J Med 1986;81:255–259.
14. Rosendaal FR, Cannegetier SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993;69:236–239.
15. Fleiss JL. Statistical methods for rates and proportions. 2nd edition. New York: John Wiley; 1981. p 14–15.
16. Kaplan EL, Meier P. Nonparametric estimation for incomplete observations. J Am Stat Assoc 1958;53:457–481.
17. Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 1978;35:1–35.
18. Cox DR. Regression models and life-tables. J R Stat Soc 1972;34: 187–220.
19. Meschengieser SS, Fondevila CG, Frontroth J, Santarelli MT, Lazzari MA. Low intensity oral anticoagulation plus low-dose aspirin versus high-intensity oral anticoagulation alone: a randomized trial in patients with mechanical prosthetic heart valves. J Thorac Cardiovasc Surg 1997;113:910–916.
20. Landefeld CS, Rosenblatt MW, Goldman L. Bleeding in outpatients treated with warfarin: Relation to the prothrombin time and important remediable lesions. Am J Med 1989;87:153–159.
21. Fondevila C, Meschengieser S, Lazzari MA. Amiodarone potentiates acenocoumarin. Thromb Res 1988;52:203–208.
22. Altman R, Rouvier J, Gurfinkel E, D'Ortencio O, Manzanel R, de la Fuente L, Favaloro R. Comparison of two levels of anticoagulant therapy in patients with substitute heart valves. J Thorac Cardiovasc Surg 1991;101:427–431.
23. Butchart EG, Lewis PA, Bethel JA, Breckenridge IM. Adjusting anticoagulation to prosthesis thrombogenicity and patient risk factors. Circulation 1991; 84:III-61–III-69.